

## REMARKS

Claims 1-6 and 29-31 are pending in this application. Claims 1-6 and 29-31 have been rejected. By this amendment, claim 2 is amended.

### **REJECTIONS UNDER 35 U.S.C. §103(A)**

#### **Independent Claims 1 and 29 and Dependent Claim 30**

Independent claims 1 and 29 and dependent claim 30 were rejected under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent No. 5,843,657 to Liotta et al. (hereinafter “Liotta”) in view of U.S. Patent No. 4,333,983 to Allen. (hereinafter “Allen”) and U.S. Patent No. 4,508,435 to Graham et al. In particular, the Office states:

Liotta does not disclose a translation stage including a vacuum chuck having a beam path hole. Allen discloses a device comprises: a translation stage 22 (fig 3) including a vacuum chuck 21 (fig 3). Graham discloses a vacuum chuck for a microscope comprising: a beam path hole 120 (fig 4). It would have been obvious to modify Liotta with Allen’s device and Graham’s vacuum chuck to control the movement of the sample easier and it would have been obvious to modify Allen with Graham’s vacuum chuck having a beam path hole to perform the LCM without removing the sample from the vacuum chuck to make the system more accurate.

Liotta does not explicitly disclose placing the LMC transfer film on the sample with a pressure sufficient to allow the LCM to transfer the selected sample. However, the skill artisan would have been motivated to use only sufficient pressure so that it does not destroy the sample.

(Office Action, pg 2-3).

Applicants traverse this rejection. In order to establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference must teach or suggest all the claim limitations. MPEP §2143.

With respect to independent claims 1 and 29 and dependent claim 30, in order to establish a prima facie case of obviousness, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art

to modify the reference or to combine reference teachings. Applicants maintain that there is no suggestion or motivation in Allen or Liotta or in the knowledge generally available to one of ordinary skill in the art to modify Liotta so as to include the translation stage of Allen or to combine Liotta and Allen. Allen discloses a translation stage which is “driven in a reciprocating fashion” (Allen, col. 5, lines 22-23) for the purpose of moving an indenter 26 with a spherical tip to scratch test an optical coating (Allen, col. 5, lines 8-28). A scratch tester is opposed to an LCM instrument of the present invention and that described in Liotta and there is no suggestion or motivation found in Allen or Liotta to combine the translation stage for a scratch tester with the LCM apparatus of Liotta especially without rendering one or the other useless for their intended purpose. For these reasons, independent claims 1 and 29 and dependent claim 30 are non-obvious.

Furthermore, the prior art must teach or suggest all the claim limitations. The prior art does not teach or suggest the limitations of (1) placing the transfer film with sufficient pressure, (2) placing the transfer film without forcing non-specific transfer, and (3) transferring a portion of the sample to the transfer film without forcing non-specific transfer. The Office acknowledges that Liotta does not explicitly disclose placing the transfer film on the sample with a pressure sufficient to allow the LCM to transfer the selected sample (Office Action, pg. 3), but argues that a skilled artisan would have been motivated to use only sufficient pressure so that it does not destroy the remaining sample. Knowledge generally available to one of ordinary skill in the art can be used to provide suggestion or motivation to modify the reference or to combine reference teachings under prong one of the obviousness determination, but it cannot be used to teach or suggest claim limitations under prong three of the analysis. The prior art reference must teach or suggest all the claim limitations. The prior art does not teach or suggest the limitations of (1) placing the transfer film with sufficient pressure, (2) placing the transfer film without forcing non-specific transfer, and (3) transferring a portion of the sample to the transfer film without forcing non-specific transfer. Applicants respectfully request the Office to provide specific citation to the already-cited prior art or new prior art for such teaching or suggestion.

The independent claims recite placing and transferring without non-specific transfer. This limitation is not disclosed, taught or suggested in the prior art. In particular, the first point is that the need to modify the LCM system to prevent non-specific transfer of the tissue was not obvious. With respect to Figure 8d in Liotta, only the portions of the tissue

selected by the laser are shown to be attached to the laser capture microdissection film. Figure 8d is a highly idealized representation of LCM, which shows the original hope of the inventors that they would be able to remove only the portions of the tissue selected with the laser. The drawing of Figure 8d is idealized in a number of respects. For one, tissue samples are not flat as shown. The figure also does not represent the true nature of the tissue, which is friable material that can easily fracture and break into small pieces, which can adhere to the plastic film in areas where the film has not been activated.

Liotta did not appreciate the problem of non-specific transfer at the time of filing. One piece of evidence that the Liotta inventors did not originally realize the problem with non-specific transfer of tissue is the fact that they subsequently realized the problem and filed patent applications on ways to avoid non-specific transfer. For example, see PCT application WO0034757A1.

The state of the art at that time was placing a free-standing film onto a tissue sample by hand. The freestanding film is similar in feel to a piece of Saran Wrap™ or a plastic sandwich bag. If this freestanding film were dropped onto the tissue section, in most cases LCM would not work because the film would not be in adequate contact with the tissue. Instead of just dropping the film on the tissue, the LCM users at that time would rub the film down onto the section with thumb or fingers much as one would press down on tape to make it adhere.

This method of pressing down the transfer film with the finger turns out to be problematic and its problems led to the inventions described in this patent application. The finger pressure is uncontrolled, and leads to the worst of both worlds in that some portions of the film are not pressed with sufficient pressure in order to allow LCM to occur, other portions of the film are pressed too much, resulting in extreme non-specific transfer.

When inventors of the present invention began to build a system meant for commercialization of the technology, they realized the problems with the existing methods. They realized that the product was not going to be viable if the transfer film were placed manually. The realization of this problem led to the invention and its various embodiments described in the application. First, the inventors uniquely realized the importance of controlling the pressure on the transfer film and the importance of not applying too much force or non-specific transfer would occur, and also the importance of applying too little force because LCM transfer in the selected regions would not occur. They also realized that the pressure applied to

the film must be consistent across the film in order to maximize performance. They found that it is desirable to have a carrier for the transfer film in order to control the application of this pressure.

In summary, the inventors of the present invention realized problems with LCM not appreciated by others at the time and invented ways of performing LCM including providing a carrier for the film and automating the placement of the carrier in ways that maximize the ability of LCM to pick up tissue and to minimize non-specific transfer of unwanted portions of the tissue. For these reasons and for the reason that the prior art does not disclose, teach or suggest all of the claim limitations, applicants believe that independent claims 1 and 29 and dependent claim 30 and their respective dependent claims are non-obvious and in a condition for allowance.

### **Dependent Claim 2**

Applicants have amended dependent claim 2 to clarify the invention. Claim 2 now recites that the step of translating the sample holder with regard to said translation stage when a vacuum is engaged wherein there is a leakage between said sample holder and said translation stage adapted to control a force holding said sample holder in place. No new matter has been added.

With respect to dependent claim 2, applicants believe that at least the third criterion listed above is not met and maintain that the prior art references do not disclose, teach or suggest all the claim limitations. The third criterion states that the prior art references must teach or suggest all of the claim limitations in order to establish a prima facie case of obviousness. MPEP § 2143. Claim 2, as amended, recites translating the sample holder with regard to said translation stage when a vacuum is engaged wherein there is a leakage between said sample holder and said translation stage adapted to control a force holding said sample holder in place. The prior art does not disclose, teach or suggest at least this claim limitation. A sample holder is movable, for example, to locate a portion of the sample on the sample holder within an optical axis. It is advantageous in laser capture to have a sample holder that is movable *with* the translation stage and/or movable *with respect to* the translation stage during any stage of the process.

The references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination. MPEP §2141. This tenet must be adhered to when applying 35 U.S.C. §103. MPEP §2141. Applicants maintain that there is no disclosure,

suggestion, or motivation in the references to make a sample holder movable with respect to the translation stage when the vacuum is engaged. In fact, Graham teaches away from this claim limitation. In particular, Graham employs stop members 116-118 which are positioned on surface 114. “The stop members 116-118 are positioned on surface 114 to interferingly engage the two edges of a conventional 1 inch by 3 inch microscope slide (denoted by reference designation 120 in FIGS. 3-5) and locate the slide adjacent to the slide supporting surface 114 in a predetermined orientation.” Graham col. 3 lines 18-25. For these reasons, the teachings of the references are not sufficient to render the rejected claims *prima facie* obvious. MPEP §2143.01.

Furthermore, the feature of the vacuum chuck being adapted so that the sample holder is movable with respect to the translation stage when the vacuum chuck is engaged provides significant advantages not known to one of ordinary skill in the art at the time the invention was made. For example, one advantage is that this feature allows for the sample holder to be moved and yet remain fixed after being moved. This movement permits tactile control of the sample holder that is independent of the movement provided by the translation stage while the vacuum chuck is engaged. A user of the instrument can move the sample holder by hand while the vacuum chuck is engaged and then for example use a joystick to move the translation stage and vice versa. This feature allows movement of the sample holder when the vacuum is engaged with or without moving the translation stage. Furthermore, keeping the vacuum chuck engaged while moving the sample holder provides advantages such as helping to prevent displacement of any transfer film carrier located on the sample holder during movement. Accidental displacement of a transfer film carrier can result in the unwanted non-specific transfer of tissue to the transfer film. The force provided by the vacuum can help prevent or counteract such displacement.

### **Dependent Claims 3-6**

With respect to dependent claims 3-6, the Office states that:

Allen does not disclose how to use a force to move the sample holder as claimed. However, it would have been obvious to modify Allen’s system with different methods to move the sample holder or to move the sample holder in different directions for different uses. The modification only involves routine skill in the art.

Office Action, pg. 3.

Applicants traverse this rejection. The prior art must teach or suggest all the claim limitations. The Office acknowledges that “Allen does not disclose how to use a force to move the sample holder as claimed” (Office Action, pg. 3) but argues that the modification only involves routine skill in the art. Knowledge generally available to one of ordinary skill in the art can be used to modify the reference or to combine reference teachings under prong one of the obviousness analysis, but it cannot be used to provide a teaching or suggestion of claim limitations under prong three of the analysis. The prior art reference must teach or suggest all the claim limitations. The prior art does not teach or suggest at least the limitation of holding the sample holder with a force and modulating the force as recited in claim 3. In fact, Graham teaches away from moving the sample holder in any direction parallel with a top surface of the translation stage without constraint as recited in claim 6. Graham does not allow movement of the sample holder in any direction parallel with the top surface of the translation stage without constraint. Instead, Graham employs stop members 116-118 which are positioned on surface 114. “The stop members 116-118 are positioned on surface 114 to interferingly engage the two edges of a conventional 1 inch by 3 inch microscope slide (denoted by reference designation 120 in FIGS. 3-5) and locate the slide adjacent to the slide supporting surface 114 in a predetermined orientation.” Graham col. 3 lines 18-25. For these reasons, the teachings of the references are not sufficient to render the rejected claims *prima facie* obvious. MPEP §2143.01.

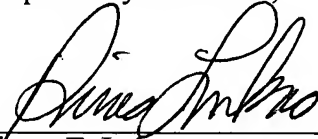
For the reasons discussed above and because several elements are not disclosed, taught or suggested in the prior art independent claims 1 and 29 and their corresponding dependent claims are believed to be nonobvious and in a condition for allowance.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, Applicant petitions for any required relief including extensions of time. The Examiner is invited to contact the undersigned attorney with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,

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